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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,444	10/24/2005	Dayuan Wang	58260-011600/US	4302

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EXAMINER	
RAHMANI, NILOOFAR	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/528,444	WANG ET AL.	
	Examiner	Art Unit	
	Niloofar Rahmani	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-36 are currently pending in the instant application.

Priority

2. This application is file on 10/24/2005, which is a 371 of PCT/CN03/00748, filed on 09/04/2003, which claims the priority of CHINA 021306869, filed on 09/18/2002.

3. *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-11, 14-18, 19-28, and 30-34 provide for the use of immunosuppressive agent or anti-inflammatory agent but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

4. *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 7-11, 14-18, 19-28, and 30-34 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*,

153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

5. *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4, 6, 13, and 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "a method for preparation of the compound" is confusing. There is no reaction step to prepare the compound comprising the step of reacting the first lead compound triptolide with $POCl_3$, PCl_3, or other phosphonate halide, phosphate, phosphite halide, phosphite. Correction is required.

6. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-11, 14-18, 19-28, and 30-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for arthritis disease and heart transplanted with WDY6 and WDY7, does not reasonably provide enablement for treating any other claimed diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims.
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims: The claims have drawn to method of using the compounds of formula I, II, IIIa, IIIb as anti-inflammatory agent or immunosuppressive agent. These include thousands of different diseases. This is a broad breadth of claims.

The nature of the invention: The instant invention is drawn to method of using the compounds of formula I, II, IIIa, IIIb for treating inflammatory or immunosuppressive diseases

The state of the prior art: The Dinitrochlorobenzene (DNCB) model of inflammatory or immunosuppressive disease is not predictable of clinical efficacy for treating inflammatory diseases generally. " Experimental model of contact sensitivity to dinitrochlorobenzene (DNCB) in inbred AO rats was employed to determine both antigen (hapten)-specific as well as parameters of antigen-non-specific aspects of contact hypersensitivity (CHS) response. All the dose of DNCB employed for the elicitation of CHS in sensitized animals, increased activity of peripheral blood granulocytes which activate of both antigen (hapten)-specific and innate immunity in contact hypersensitivity." (Kataranovski et al., determatovenerologica, 2001, Vol. 10, pages 1-10).

The Cotton ball model of inflammatory or immunosuppressive disease is not predictable of clinical efficacy for treating inflammatory diseases generally. " Three animal models to induce experimental inflammation in rats, including carrageenin-induced paw edema, cotton-ball granuloma and adjuvant induced arthritis, were chosen to study the anti-inflammatory effect of the TCM (Traditional Chinese Medicine) agent." (Wei et al., Zhongguo Zhong Yao Za Zhi, 2002, Vol. 27(3), pages 215-8). This Cotton-ball assay is only used in China and nowhere outside the China, is used.

The level of the skill in the art: The artisan using Applicants invention would be a physician with a MD degree and several years of experience.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In*

re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the pharmaceutical composition combining of formula I, II, IIIa, IIIb would be used for treating any and all inflammatory or immunosuppressive diseases.

The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Amount of guidance/working examples: On pages 16-17 of the specification, applicant has example of doses up to 15 mg/kg of WDY1, WDY6, WDY7 compounds using Dinitrochlorobenzene (DNCB) model, which administered on the naked skin to sensitize animal with arthritis diseases and on page 19 of the specification, applicant has example of doses up to 40 mg/kg x 8 of WDY1, WDY6, WDY7 compounds using Cotton-ball model. On pages 16, and 18 of the specification, applicant has rat's models of arthritis diseases such as Dinitrochlorobenzene (DNCB) model and Cotton-ball model. On page 21, Table 6

and page 23, Table 8 of the specification, applicant disclosed the compounds WDY6, WDY7 using for treating arthritis diseases and heart transplanted.

The quantity of experimentation needed: The quantity of experimentation is large because of the combination of two ingredients would have been to be formulated into a dosage form. The proper ratio and amount of these two ingredients found and this formulation tested in the clinic or in an assay known to be correlated to clinical efficacy. This is a large quantity of experimentation.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Taking all of the above into consideration, it is not seen where the instant claims 7-11, 14-18, 19-23, 24-28, and 30-34 for treating inflammatory diseases or causing immunosuppressive, have been enabled by the instant specification.

7. *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 3 is rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. WO 00/63212. Wang et al. disclosed the instant claimed compound on pages 2-3, wherein R_1 being alkyl having 1-4 carbon atoms, $-C(=O)(CH_2)_nCO_2$, wherein n being 1-4 and R_2 being -SCN. Therefore, the instant claim is anticipated by Wang et al.

8. Claim 3 is rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al., Yaoxue Xuebao, 1992, Vol. 27(11), pages 830-6. Zhang et al. disclosed the instant claimed compound on page 831, compound 7, wherein R_1 being AC, and R_2 being Cl. Therefore, the instant claim is anticipated by Zhang et al.

9. ***Claim Objections***

Claim 29 is objected to as being dependent upon a withdrawn base claim, but would be allowable of rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. ***Allowable Subject Matter***

Claims 1,5,12 are patentable over Wang et al. WO 00/63212. The reference teaches six fused rings instead of the seven fused rings compounds of the instant application. Therefore, the claims are free of prior art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas Mckenzie, can be reached on 571-272-0670. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI

06/15/2006

NR

THOMAS MCKENZIE

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